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Communal nesting exerts epigenetic influences on affective and social behaviors in rats selectively bred for an infantile trait

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HIGHLIGHTS

- We examined a model of communal nesting in rats from two lines bred for infantile affect.
- Communal nesting decreases neonatal distress calls in the high anxiety line.
- Communal nesting increases parenting and play in juveniles of both lines.
- Communal nesting decreases anxiety and depression in adults of both lines.
- Communal nesting increases activity in the Low line.
- Rat CN/Line model may be useful for studying epigenetic effects of early enrichment.

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ABSTRACT

Communal nesting (CN) is a mouse model of early social enrichment during pregnancy and lactation. In this study, a rat model of CN was developed to determine if CN exerts an epigenetic effect in rats selectively bred for an infantile affective trait (high and low rates of ultrasonic distress calls). High and Low offspring from CN groups were compared to standard reared (SN) offspring on five measures of social and affective behavior at three critical ages. A differential effect of the CN paradigm on High and Low lines was seen in measures of anxiety and arousal, but not in measures of depression or social behavior. Neonatal CN subjects emitted fewer distress calls than SN subjects when separated from their dams, and the High line subjects were more affected by the CN procedure. As juveniles, CN subjects showed increased social behaviors in tests of juvenile parenting and play compared to SN subjects. In adulthood, CN differentially increased the activity of Low line subjects. All CN subjects displayed less anxiety behavior in an open field compared to SN subjects; High line subjects were more anxious than Lows. CN reduced immobility and increased attempts to escape on the Porsolt forced swim task relative to SN subjects. These results extend the usefulness of this early enrichment paradigm from mice to rats, and found some rodent species differences in outcomes dependent on the behavioral test. They also emphasize the importance of social contact during pregnancy and lactation on offspring's optimal development across behaviors and ages.

1. Introduction

An understanding of the active regulation of gene expression by environmental influences (epigenetics) through animal models is essential for determining underlying mechanisms of psychiatric disorders. Early environment has been implicated in shaping multiple aspects of behavior, including affect, learning, addiction, and social interactions. Parental care and peer interactions can act as epigenetic factors in development [1–4]. In older animals, impoverished social environments can induce cognitive, physiological, and social deficits while enriched social environments can enhance cognition and ameliorate the detrimental effects of stressors [5,6]. The affective and cognitive benefit provided by enriched housing is heavily dependent upon access to social interactions [7].

1.1. Communal nesting paradigm

Communal nesting (CN) is a unique paradigm implementing social enrichment from birth through weaning. The CN paradigm has been explored as a form of preweaning environment enrichment in which three female mice are mated with the same male, gestate together, and rear their litters together until weaning [8–10]. The preweaning enrichment

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allows dams to share care-giving behaviors and establishes a social experience that more closely imitates rodents' natural rearing environment [11]. In the standard laboratory rearing conditions (SN), pregnant mice are housed separately throughout gestation and lactation. In this mouse model, CN reared offspring demonstrate environmentally-induced variations in behavior on measures of depression, anxiety, novelty seeking, and social behavior in adulthood (8–10, 12, 13).

This socially enriching CN paradigm produces particularly salient effects on behavior during social tasks; social interactions reveal a significant reduction in the time necessary to establish a social hierarchy within CN adult males relative to standard nesting (SN) males [9]. Characteristic dominant or submissive behaviors are adopted during the first social encounter by CN subjects; SN controls typically require five encounters to fully establish a dominant and submissive relationship within a pairing [9]. Adult CN females also exhibit decreased vocalizations and anogenital sniffing of novel females in the social recognition task compared to SN females [14]. In addition, CN female mice display greater maternal behavior and are less aggressive in the intruder test [15].

The CN paradigm in mice also appears to alter affective behavior. Male mice reared in a communal environment demonstrated greater depressive behavior, indicated by shorter durations to and longer durations of immobility on the Porsolt forced swim test [10]. CN males also displayed increased anxiety behavior relative to SN males, as seen in increased thigmotaxis on the open field maze [8,10], longer latencies to approach a novel object and reduced time in the open arms of the elevated plus maze [8,10], and reduced head-dipping [13]. Communal rearing was not reported to increase anxiety in adult female mice, but did decrease indices of depression as seen in isolation-induced sucrose preference and floating time in the Porsolt forced swim test [14]. In contrast to these results, restricting the communal rearing period to post-parturition, without the communal gestation phase, resulted in male offspring who displayed less anxiety as measured by open arm entries on the plus maze, and no difference from control reared offspring in the Porsolt forced swim test [16].

1.2. Selective breeding of High and Low vocalizing lines

Rodents emit ultrasonic vocalizations (USVs) in distinct frequency ranges (30–90 kHz); these vocalizations are indictors of affect, and elicit or inhibit social behavior [17]. For example, USVs of 55 kHz are recorded during rough-and tumble play [17–19]. Vocalization rates increase upon interruption of a play session and remain elevated when juveniles are isolated [17]. Infant rats vocalize when separated from their dam and littermates, and stop vocalizing when reunited with the dam [20]. Pup-emitted vocalizations prompt retrieval by the dam and direct maternal behaviors, such as increased anogenital licking, which are critical to optimal pup development [21,22]. Exposure to infant vocalizations stimulates virgin females to engage in nest building [21]. These infant vocalizations, which range between 40 and 55 kHz, persist for approximately the first 3 weeks of life [23]. Selective breeding of rats whose USV rates were quantified as neonates as vocalizing at the highest and lowest rates produced two distinct lines, called High and Low [24,25]. The High and Low lines not only differ in USV rates, but behavioral phenotypic differences were found to persist into adulthood. The High line demonstrates an anxious and depressive phenotype, and the Low vocalizing strain displays an aggressive and low affect phenotype [25–27].

We were interested in whether the genetically-determined affective temperaments seen in the High and Low lines might interact with the environmentally-induced effects of the CN manipulation. We were also interested in whether the effects of CN in rats differed from those in mice, and whether detected sex differences in mice would be evident in rats. The behavioral measures examined ranged from neonatal to adult ages, and included affective (USVs, open field, and forced swim) and social (juvenile play and juvenile parental care) tests.

2. Materials and methods

2.1. Subjects

Subjects were NIH Norway rats derived from the 25th generation of the High and Low lines [28] raised in Williams College animal facilities. Subjects were given unlimited access to food and water, and were double housed with a same sex sibling in standard hanging cages prior to breeding. Lights were set to a 12:12 hour cycle. Colony temperatures were maintained at 22 °C with 50% relative humidity. All housing and testing procedures were approved by the Williams College Institutional Animal Care and Use Committee. Only one male and one female from any communal or standard litter were tested on each behavioral task. No subjects were tested on more than one test. Testing was conducted between 1100 and 1700 h, with the exception of the Play Test, which was conducted between 1900 and 2000.

2.2. Gestation/lactation housing conditions

2.2.1. Standard nesting

One male and one female of the same line were mated within the male's hanging cage. The following morning, pregnant females, as indicated by the presence of a plug, were removed and singly housed in a standard tub cage (43 cm × 22.5 cm × 21 cm). Females remained undisturbed throughout the remainder of their pregnancy with the exception of twice weekly bedding changes. Naive subjects were weaned at PN25 with a littermate (e.g. same-sex, same line) into a hanging cage.

2.2.2. Communal nesting paradigm

Three females and one male of the same line were bred in a communal cage (55 cm × 27 cm × 28 cm). The male was removed after 16 days. Communal groups remained undisturbed with the exception of twice weekly bedding changes. Naive subjects were weaned at PN25 with a littermate (e.g. same-sex, same line) into a hanging cage

2.3. Behavioral tests

2.3.1. Ultrasonic vocalizations (USVs)

Subjects (one male and one female) for the USV Test were selected at random from each litter at PN 6 and taken to a dimly lit adjacent room in a plastic cage (28 cm × 17.5 cm × 12.5 cm) filled with fresh bedding. The cage was placed on a heating pad set at 32 °C. After 20 min, a subject was placed individually in a circular glass dish (10 cm × 20 cm diameter). Suspended over the container was an S-25 ultrasound bat detector (Ultra Sound Advice, London) set to detect signals at 45 ± 5 kHz. Ultrasonic vocalizations (USVs) were counted for 2 min by listening through earphones attached to the bat detector. Subjects were weighed after testing.

2.3.2. Juvenile parenting test

Subjects (one male and one female) for the Juvenile Parenting Test were selected at random from each litter at PN 22, weighed and housed together for the duration of the testing. The retrieval test consisted of two attached Plexiglas compartments: a 43 cm × 22.5 cm × 21 cm main compartment and a 33 cm × 16.5 cm × 14 cm retrieval box, with a transparent sliding door divided the two compartments. For each subject, three pups (5 ± 2 days old) of a randomly-bred control line served as “targets” for parental behavior. At PN 22, the subject was placed in the main compartment with the three target pups for one hour to habituate to the testing chambers. The sliding door dividing the two compartments was open, enabling subjects to explore the entire apparatus.